Health economics of direct oral anticoagulants in the Netherlands

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Chapter 10 - Discussion

In 2008, for the first time since the 1950s, a new type of oral anticoagulants was introduced to the market concerning the class of direct oral anticoagulants (DOACs). DOACs provide an alternative to the previous gold, standard vitamin K antagonists (VKAs). One of the main advantages of DOACs over VKAs is that they do not require monitoring of the international normalised ratio (INR). The drawback of this is that there is less control over adherence, which has caused concern about the real-world effectiveness and safety of DOACs. There has also been a lot of discussion around the costs of the DOACs as compared to VKAs.

In a report from the Health Council of the Netherlands from 2012, it was estimated that the annual drug costs of the DOAC dabigatran were four times as high as the combined costs of acenocoumarol and INR monitoring (€1,000 versus €225 per year, respectively) [1]. On the other hand, there is more and more (real-world) evidence suggesting that DOACs are associated with a better risk/benefit balance compared to VKAs, which has a beneficial effect on a patient's health and healthcare costs. Cost-effectiveness analyses enable to analyse whether this difference in risk/benefit balance outweighs the difference in drug and monitoring costs.

Because of the relatively high budget impact, the Health Council of the Netherlands opted for a gradual and conservative introduction of DOACs and recommended careful monitoring and documentation of bleeding and thrombotic complications. Meanwhile, the Dutch government asked for the investigation of safety data and cost-effectiveness in the real-world setting as complement to the available trial data. As a response, the aim of this thesis was to demonstrate the economic consequences of the broad implementation of DOACs in the Netherlands, by using real-world data (RWD) to validate the trial-based outcomes cost-effectiveness analyses comparing DOACs and VKAs in the general atrial fibrillation (**part I**) and venous thromboembolism (**part II**) populations, as well as modelling specific subgroups that may have been excluded in the initial registration trials. With this and in hindsight, we address the question of whether the conservative introduction of DOACs based on the argument of high costs was justified.

What is the cost-effectiveness of DOACs in patients with atrial fibrillation and venous thromboembolism in the Netherlands?

Table 1 presents an updated version of the overview of published cost-effectiveness analyses of DOACs in the Netherlands up to the year 2020, including the chapters of this thesis. As mentioned in the introduction, the ICERs are generally higher in patients with atrial fibrillation compared to patients with venous thromboembolism, which can be explained by the difference in treatment duration. Atrial fibrillation is a chronic disease that requires continuous protection against arterial thromboembolism, while venous thromboembolism—in most trials—is treated with three to twelve months of anticoagulation. On the other hand, longer anticoagulation use also leads to an increase in the QALYs gained.

Over a lifetime horizon, the ICER in patients with atrial fibrillation, is around €10,000–€20,000/QALY. Compared with the willingness-to-pay threshold of €20,000/QALY suggested for the Netherlands, treatment with DOACs in patients with atrial fibrillation can be considered cost-effective. There are some recent studies suggesting that the ICER may even be lower. In chapter 3 of this thesis, apixaban was shown to be cost-effective compared to VKAs, with an ICER of €3,506/QALY in the network meta-analysis (NMA-) based analysis [2]. One other study even suggested that dabigatran is dominant (cost-saving and more effective) over VKAs in patients with atrial fibrillation [3]. These cost savings were mainly driven by indirect costs of production losses.

In patients with venous thromboembolism, the ICER is mostly found to be cost-saving, but as mentioned before, the ICER is highly dependent on the treatment duration. As shown in chapter 7 of this thesis, lifelong treatment duration with apixaban resulted in an ICER of €9,653/QALY compared to LMWH/VKA. However, this would still be cost-effective at a willingness-to-pay threshold of €20,000/QALY. The ICER presented in the pharmacoeconomic dossier of rivaroxaban was not cost saving, but can be considered highly cost-effective at €5,896/QALY. As also already mentioned in the introduction findings of non-cost-savings for the thromboembolism indication may be explained by the exclusion of the non-medical indirect costs, such as productivity losses.

The difference in price between DOACs and VKAs is one of the main drivers of the difference in cost-effectiveness. Long-term use of anticoagulation leads to an increasing difference in drug costs and, therefore, higher total costs in the long run. In all chapters, the drug prices were based on the publicly available list prices. However, there have been confidential price arrangements in place for DOACs since 2013 in the context of a price/volume patient access scheme [4]. Therefore, the ICERs are likely to be overestimated. Of course, the costs of VKAs and INR monitoring may also differ in reality compared to the publicly available prices. Nevertheless, it is to be expected that the expiration of the patents for the NOACs will massively reduce the ICER.

Do the RWD-based cost-effectiveness analyses confirm the findings of the trial-based cost-effectiveness analyses?

Atrial fibrillation

Cost-effectiveness of rivaroxaban compared to VKAs in patients with atrial fibrillation was assessed in **chapter 2** using RWD gathered during one year. The cost-effectiveness model was based on the single-arm real-world study XANTUS (NCT01606995) and was limited to a time horizon of one year [5]. The frequency of INR monitoring was based on RWD from the annual report of the Federation of Dutch Thrombosis Services (FNT, *Federatie van Nederlandse Trombosediensten*) [6]. In the base case analysis, we based the frequency of INR monitoring on the total atrial fibrillation population of the Netherlands. Compared to VKA treatment, rivaroxaban treatment was associated with a gain of 0.018 QALYs and extra costs of €48.44 per patient over a period of one year, resulting in an ICER of €2,628/QALY. In the scenario analyses, the cost-effectiveness of rivaroxaban compared to

VKAs in two subpopulations specified in the annual report of the FNT [6] was assessed: patients with unstable INR and patients who measure or -monitor their INR themselves. In both scenarios, rivaroxaban appeared to confer health gains and cost-savings compared to the VKA.

There were three trial-based cost-effectiveness analyses on rivaroxaban compared to VKAs in patients with atrial fibrillation published (Table 1). The pharmacoeconomic dossier published by *Zorginstituut Nederland* presented an ICER of €11,396/QALY from a societal perspective [7]. Two other cost-effectiveness analyses from a healthcare payer's perspective showed higher ICERs (€24,124/QALY and €34,248/QALY) [8,9]. It is difficult to compare the results of these analyses with our RWD-based analysis because of, the difference in time horizon (lifetime versus one year, respectively). However, given the results of chapter 2, there is no reason to suspect that the cost-effectiveness in a real-world situation differs from the initially calculated trial-based cost-effectiveness.

In **chapter 3**, we evaluated the cost-effectiveness of apixaban against other DOACs (dabigatran, edoxaban and rivaroxaban) and VKAs as a stroke-prevention treatment in patients with atrial fibrillation by collating the available data from both randomised clinical trials (RCT) and real-world analyses of all DOACs into one integrative previously published model. The RWD-based analysis was specifically implemented using externally validated findings from an NMA-based analysis, which was based on RCT data. The RWD was identified through a systematic literature search in Pubmed. The real-world study ARISTOPHANES was considered most appropriate because it satisfied all predefined eligibility criteria. This study included 434,046 AF-patients on warfarin, apixaban, dabigatran, and rivaroxaban.

Table 1. Overview of cost-effectiveness studies published before the publication of the first project in this thesis.

	Author [ref] Publication date	Intervention	Comparator	Perspective	Treatment duration	Time horizon	Δcosts*	ΔQALYs*	ICER (€/QALY)
Atrial fibrillation	Health Council of the Netherlands [1] 15-5-2012	dabigatran	VKA	Healthcare payer	Continuous	Lifetime	€3,057	0.260	€11,758[a]
							€3,080	0.260	€11,846[b]
							€4,401	0.220	€20,375[c]
							€3,370	0.150	€23,082[d]
	ZIN [10] 6-6-2012	dabigatran	VKA	Societal	Continuous	Lifetime	€2,111	0.158	€13,332
	ZIN [7] 26-10-2012	rivaroxaban	VKA	Societal	Continuous	Lifetime	€2,102	0.184	€11,396
	Le et al. [8] 22-10-2013	apixaban	VKA	Healthcare payer	Continuous	Lifetime	€3,746	0.300	€12,488
		dabigatran					€3,765	0.310	€12,146
		rivaroxaban					€5,066	0.210	€24,124
	Stevanovic et al. [11] 5-8-2014	apixaban	VKA	Healthcare payer	Continuous	Lifetime	€1,852	0.180	€10,576
	Verhoef et al. [9] 18-12-2014	apixaban	VKA	Healthcare payer	Continuous	Lifetime	€4,754	0.365	€13,024
		dabigatran					€5,465	0.374	€14,626
		rivaroxaban					€5,681	0.166	€34,248
	Van Hulst et al. [3] 7-9-2017	dabigatran	VKA	Societal	Continuous	Lifetime	€1,389	0.455	Dominant
	Jacobs et al. [12] 27-11-2017	rivaroxaban	VKA	Societal	At least 9-10 weeks	1 year	€1,83	0.230	€7.92
	De Jong et al. [13] 15-1-2019	rivaroxaban	VKA	Societal	Continuous	1 year	€48.44	0.018	€2,628
	Bennaghmouch et al. [14] 1-4-2019	DOAC + APT	VKA + APT	Healthcare payer	Continuous	1 year	€357	0.017	€20,919

Table 1. Overview of cost-effectiveness studies published before the publication of the first project in this thesis. (continued)

	Author [ref] Publication date	Intervention	Comparator	Perspective	Treatment duration	Time horizon	Δcosts*	ΔQALYs*	ICER (€/QALY)
Atrial fibrillation	De Jong et al. [2] 17-9-2019				NMA-based analysis				
		apixaban	VKA	Societal	Continuous	Lifetime	€920	0.262	€3,506
			dabigatran 110 mg				€-2,692	0.177	Dominant
			dabigatran 150 mg				€-819	0.131	Dominant
			edoxaban				€-1,027	0.101	Dominant
			rivaroxaban				€-197	0.065	Dominant
					RWD-based analysis				
		apixaban	dabigatran	Societal	Continuous	Lifetime	€-672	0.285	Dominant
			edoxaban				€-2,098	0.216	Dominant
			rivaroxaban				€-1,966	0.137	Dominant
Venous thromboembolism	ZIN [7] 26-10-2012	rivaroxaban	LMWH/VKA	Societal**	3-12 months***	Lifetime	€300	0.051	€5,896
	ZIN [15] 8-6-2015	dabigatran	LMWH/VKA	Societal	24 months	Lifetime	€-1,996	0.058	Dominant
	van Leent et al. [16] 4-8-2015	dabigatran	LMWH/VKA	Societal	6 months	6 months	€-18.90	0.041	Dominant
	Stevanovic et al. [17] 24-10-2016	dabigatran	LMWH/VKA	Societal	24 months	Lifetime	€-2,168	0.034	Dominant
	De Jong et al. [18] 1-2-2017	apixaban	LMWH/VKA	Societal	6 months	Lifetime	€-236	0.044	Dominant
	Heisen et al. [19] 25-6-2017	rivaroxaban	LMWH/VKA	Societal	3-12 months***	Lifetime	€-304	0.047	Dominant
	De Jong et al. [20] 7-8-2018	apixaban	LMWH/VKA	Societal	Continuous	Lifetime	€3,468	0.359	€9,653
	De Jong et al. [13] 15-1-2019	rivaroxaban	LMWH/VKA	Societal	6 months	1 year	€-398	0.035	Dominant
	De Jong et al. **** NA	rivaroxaban	LMWH	Societal	6 months	5 years	€-1,310	0.012	Dominant

* per patient; ** Excluding indirect non-medical costs; *** Based on the EINSTEIN trial the patients were treated either 3, 6 or 12 months. This distribution was used the calculate the cost-effectiveness; **** See chapter 9 of this thesis; [a] Based on NL model; [b] Based on model RE-LY; [c] Based on model RE-LY/Pink et al.; [d] Based on Pink et al. Abbreviations: APT, antiplatelet therapy; DOAC, direct oral anticoagulant; ICER, incremental cost-effectiveness ratio; LMWH, low-molecular weight heparin; NA, not applicable; QALY, quality-adjusted life years; VKA, vitamin K antagonist; ZIN, *Zorginstituut Nederland*.

In the NMA-based analysis, apixaban appeared to be cost-effective compared to VKAs and cost-saving compared to dabigatran 110 mg, dabigatran 150 mg, rivaroxaban and edoxaban. The RWD-based analysis showed that apixaban is cost saving compared to all comparators. Apixaban was shown, in both the NMA- and RWD-based analyses, to be the most cost-effective treatment option at a WTP threshold of €20,000/QALY (50% and 94%, respectively). It could be concluded that the cost-effectiveness results based on the real-world ARISTOPHANES study confirm the results based on the RCTs. It should be mentioned that only marginal differences in costs and health effects were found, especially compared to other DOACs, and the use of different effectiveness and safety data sources or assumptions, considerations of specific patient populations, and costs may lead to different outcomes.

Venous thromboembolism

The first two chapters of part II of this thesis reflect RCT-based cost-effectiveness analyses of DOACs for the treatment and secondary prevention of venous thromboembolism. The cost-effectiveness of dabigatran compared to VKAs in **chapter 5** was based on the RCTs RECOVER, RECOVER II, RE-MEDY, and RE-SONATE [21–23]. In the base case analysis, the cost-effectiveness of six months of treatment followed by 18 months of secondary prevention with dabigatran or a VKA was calculated from a societal perspective. Dabigatran appeared to be a cost saving alternative to a VKA for the treatment and secondary prevention of VTE. Patients on dabigatran gained an additional 0.034 discounted QALYs over a lifetime and savings of €1,598 compared to patients on a VKA.

In **chapter 6,** we assessed the cost-effectiveness of apixaban compared to seven days of low-molecular weight heparin followed by a VKA (LMWH/VKA) in patients who experienced a venous thromboembolic event. The model was designed based on the registration trial AMPLIFY [24]. The treatment duration in the base case analysis was six months. The ICER was calculated over a lifetime horizon from a societal perspective. Compared to LMWH/VKA, apixaban saved €236 and gained 0.044 QALYs per patient, resulting in a dominant ICER.

In **chapter 8,** we used RWD to inform the cost-effectiveness analysis. The one-year cost-effectiveness of rivaroxaban compared to LMWH/VKA in patients who experienced a VTE event was based on the real-world study XALIA [25]. Using a treatment duration of six months, rivaroxaban saved €398 and gained 0.035 QALYs per patient per year compared with LMWH/VKA, resulting in a dominant ICER. Although this analysis concerned a different DOAC, these results are highly comparable to the findings in chapter 6. It also confirms the results of the trial-based cost-effectiveness study of rivaroxaban from Heisen et al. [19]. However, since the cost-effectiveness study in chapter 8 has a one-year time horizon, the viability of a direct comparison of the results is debatable.

Because of the later market access and reimbursement approvals of the DOACs in the venous thromboembolism indication, we only have one study assessing RWD-based cost-effectiveness. Based on this one study, it is hard to confirm all trial-based cost-effectiveness analyses of DOACs in patients experiencing venous thromboembolism.

However, it is to be expected that six months treatment with a DOAC compared to a VKA in real-world setting will also convert to cost-savings, while a longer duration of 12–24 months will probably have either less cost-savings or a positive—yet cost-effective—ICER. As shown in **chapter 7**, continuous use of DOACs in patients with a high risk of recurrence is still cost-effective. However, there is no RWD-based analysis that can confirm these results.

What are the limitations of using real-world data for validation of trial-based cost-effectiveness results?

A unique aspect of this thesis is the use of RWD to validate the trial-based cost-effectiveness results. However, this can be challenging. Differences between trials and real-world studies can make the comparison of the cost-effectiveness results difficult. In this thesis we identified limitations of using RWD for validation of the registration trial-based cost-effectiveness results on two levels: limitations related to study design or limitations related to population (Table 2).

A limitation related to study design is the choice of intervention and comparator. The real-world use of anticoagulation may differ between countries. Therefore, country specific real-world studies may use different interventions and comparators than used in the registration trials. An example of this, is the use of VKA warfarin as the comparator in the phase III clinical trials of all four DOACs, whereas in the Netherlands we use VKAs acenocoumarol or phenprocoumon, not warfarin. Therefore, a Dutch real-world study would never include patients treated with warfarin. Although these VKAs are considered interchangeable, the differences in pharmacokinetics may lead to different outcomes between the VKAs [26].

Another limitation on the level of study design is related to differences in endpoints. For practical reasons, real-world studies often include less, or different, endpoints than the phase III clinical trials. Moreover, endpoints in real-world studies can be based on different definitions due to the use of different clinical guidelines. For example, the endpoint 'major bleeding' can be included in the trial as well as in the real-world study, however, definitions of major bleeding can differ.

The last limitation related to study design we identified was related to the use of propensity score adjustment. In phase III clinical trials patients are generally (double blind) randomised based on their characteristics (e.g. age, sex, risk levels), resulting in two arms with very comparable patient characteristics. In real-world practice this is often not possible. This can cause differences between the patient characteristics of the intervention and control arms of real-world studies. These differences can lead to different results. The use of propensity score adjustment to correct for differences in patient characteristics between the treatment arms can be desired. However, not all studies use this method or only use it for the primary outcomes. The use of these uncorrected endpoints to populate a cost-effectiveness model makes the interpretation of the real-world cost-effectiveness results, and consequently the comparability to trial-based cost-effectiveness results, difficult.

On a population level differences in patient characteristics between trial and real-world situation, inclusion of patients from different countries or clinical sites, and the heterogenicity of the real-world population can be a challenge for the validation of the trial data-based cost-effectiveness results. On the other hand, this is the exact reason why validation of the trial data-based results is needed. The registration trials reflect a selected portion of the population and often exclude patients who are more fragile (e.g. poor renal function, old age, high bleeding risk), while these patients are often seen in reality.

The above mentioned limitations can influence the way in which RWD is used for validation of the trial-based cost-effectiveness results. The validation can be done in two different ways: 1) by building a new cost-effectiveness model based on a real-world study (chapter 2 and 8), or 2) by updating an existing trial-based cost-effectiveness model with RWD (chapter 3). In the case of the second option, it may be appropriate to select the most eligible real-world study through a systematic literature search, as done in chapter 3. When cost-effectiveness models are designed based on real-world studies, it may often result in a different model structure given the type of data available, making the comparison to the trial-based cost-effectiveness results difficult. Ideally, by using the same model and data structure for the external validation of the trial-based cost-effectiveness, the results of both analyses could be directly compared. However, also with this approach various limitations unfortunately exist. Below we discuss the limitations we encountered in chapters 2, 3 and 8.

Table 2. Limitations of the use of real-world data for validation of trial-based cost-effectiveness results.

	Limitation
Study design	Difference in intervention (e.g., a different dose is used than in the trial)
	Difference in comparator (e.g., single-arm studies)
	Endpoints included in real-world studies are often less explicit than those of trials
	Differences in definitions of (severity of) disease or endpoints
	No or limited propensity score adjusted results available
Population	Characteristics of patients (e.g., in real-world often sicker and older)
	The patients are from other countries or clinical sites than in the trial(s)
	Heterogenicity of the population (differences in patient characteristics)

The cost-effectiveness model of chapter 2 was designed based on the real-world study XANTUS. The XANTUS study was a single-arm study, so the use of combined trial and RWD was inevitable. Data from the rivaroxaban arm of the registration trial ROCKET-AF (NCT00403767) [27] was used to match the characteristics of the patients in the XANTUS trial. With this correction, represented as matching adjusted indirect comparison (MAIC) ratios, the transition probabilities of the ROCKET-AF were corrected to reflect the XANTUS results. This provides an indirect comparison which is a limitation, but, because

there was no control group included in the XANTUS study, it was the only way to make reasonable comparisons.

As mentioned, endpoints included in the registration trials are often more explicit than those of real-world studies. Since cost-effectiveness model structures are often built based on the design and outcomes of a clinical study, the structure of the model based on RWD may differ from a trial-based cost-effectiveness model. In chapter 2, the application of the MAIC ratio was only available for the primary endpoints of the XANTUS study [28]. Because the XANTUS study only included five primary outcomes, the comparison was limited to these outcomes, and it was not possible to include, for example, the severity of an ischaemic stroke (e.g., mild, moderate, stroke) or major bleeding (e.g., intracranial vs non-intracranial haemorrhage). These factors might have contributed to either an over- or underestimation of the ICER.

In chapter 8, a decision tree model was built based on the XALIA study [25]. The event rates we used in our analysis to calculate the transition probabilities were not propensity score adjusted. The XALIA study [25] did include an analysis using propensity score-adjustment, however, in this case we decided not to use these adjusted values because they were only available for major bleeding, recurrent venous thromboembolism, all-cause mortality, major adverse cardiovascular events, and other thromboembolic events, but did not make a distinction between the types of bleeding or venous thromboembolism, which was essential to make a good estimation the ICER. The use of these propensity score adjusted risks as a basis for the health states of the RWD-based cost-effectiveness model would have led to an oversimplified cost-effectiveness model. This would make the cost-effectiveness model less representative for practice and less comparable to the trial-based cost-effectiveness studies that were previously published. The choice to use the unadjusted relative risks might have led to an overestimation of the effect of rivaroxaban and, therefore, an underestimation of the ICER. Likely however, this would not lead to a drastic change in the ICER; ergo, not changing the overall favourable cost-effectiveness profile.

In chapter 2 we updated an existing trial-based cost-effectiveness model with RWD identified through a systematic literature search. Although this approach allows for a more direct comparison of the cost-effectiveness results, a number of limitations had to be encountered in chapter 2 of this thesis. Firstly, often real-world studies are not eligible for external validation of trial-based models due the fact that not all relevant endpoints are included, or they are only presented as combined outcomes (e.g. ischaemic stroke/SE). The ARISTOPHANES study [29] included all the relevant endpoints that were part of the predefined eligibility criteria of the review, but, data on clinically relevant non-major bleeding, myocardial infarction, treatment discontinuation and other cardiovascular hospitalisations were not reported, while they were included in the model. Therefore, we had to use same event rates as in the trial-based analysis for these events.

Secondly, not all comparators in the network meta-analysis used for the trial-based analysis [30] were included in the ARISTOPHANES study [29]. The network meta-analysis presented results on both doses of dabigatran registered in Europe, while the real-world study [29] reported the combined results of different dabigatran doses. Moreover,

edoxaban was not included in the RWD because it received relatively late market access compared to the other three DOACs.

Thirdly, real-world studies include heterogeneous populations from different countries. As a result, differences in clinical outcomes can be expected, which can potentially lead to differences in economic outcomes. Therefore, results depend strongly on the choice of RWD used for external validation.

Lastly, RWD on clinical event rates in Dutch patients treated with DOACs is currently lacking. In the coming years, the recently launched project "DUTCH-AF registry" [31] aims to include 6,000 Dutch patients with atrial fibrillation and collect data on the effectiveness, adherence, and bleeding risk of DOACs and VKAs. It will be interesting to have this data of Dutch patients, since the patient characteristics, such as $CHADS_2$/CHA_2DS_2-VASc scores and age, can obviously differ among populations.

Are DOACs cost-effective in subgroups that may have been excluded from the initial registration trials?

There are patients who may have been excluded from the initial registration trials, but who may also benefit from a DOAC in practice. After registration, there were additional studies conducted to show the effect of DOACs in specific subgroups. In this thesis we assessed the cost-effectiveness of the following subgroups: patients with atrial fibrillation undergoing cardioversion, patients who need continuous anticoagulation for the prevention of venous thromboembolism, and cancer patients experiencing venous thromboembolism.

In **chapter 4**, we assessed the cost-effectiveness of rivaroxaban compared to a VKA in patients with symptomatic atrial fibrillation who undergo elective electrical cardioversion to restore the normal sinus rhythm. The patient has to receive adequate anticoagulation for at least three weeks before and at least four weeks after the procedure [32]. A one-year decision tree model was designed based on the results of the X-Vert trial [33]. The transition probabilities were obtained from the real-world study XANTUS [5]. The use of rivaroxaban was associated with a cost of €1.83 per patient and a health gain of 0.23 QALYs per patient, resulting in an ICER of €7.92/QALY. In practice, maintaining stable anticoagulation throughout cardioversion can be challenging, especially with VKAs, because the INR should be between 2.0 and 3.0. This can lead to postponement of the cardioversion, which can be overcome by using a DOAC instead of a VKA. Next to the inconvenience for the hospital and—especially—the patients, unnecessary rescheduling of the cardioversion was associated with high costs. Taken together with the fact that during a one-year follow-up rivaroxaban use resulted in a substantial increase in QALYs per person compared to use of a VKA, makes the use of DOACs in patients undergoing electrical cardioversion favourable.

As mentioned in the introduction, patients who experience a recurring VTE event (provoked or idiopathic) may require extended anticoagulation treatment. Extended treatment (secondary prevention) with apixaban was assessed in **chapter 7**. The model used in chapter 6 was adapted using data from the AMPLIFY-EXT trial [34]. In the base

case analysis, the cost-effectiveness of lifelong secondary prevention with apixaban (omitting the six months of initial treatment period) was compared with no treatment (placebo). This resulted in an ICER of €9,653/QALY. In the scenario analysis, the AMPLIFY and AMPLIFY-EXT trials [24,34] were combined: six months of initial treatment followed by lifelong secondary prevention with apixaban was compared to six months of initial treatment with LMWH/VKA followed by no treatment (placebo in the trial). This resulted in an ICER of €8,085/QALY. From chapter 5 and 6 we concluded that DOACs are very likely to be cost-effective, or even cost-saving, for the treatment and secondary prevention of VTE with a treatment duration of 6 to 24 months, but even in patients who may benefit from lifelong protection against recurring venous thromboembolism, DOACs appear to be cost-effective when compared to no treatment.

Chapter 9, consists of a cost-effectiveness and budget impact analysis of the use of rivaroxaban in patients with cancer who experienced a VTE event. Cancer patients have a temporarily provoked high risk of developing venous thromboembolism. Both the cancer itself and the cancer therapy (chemotherapy and cancer surgery) have effects on the patient's coagulation system and therefore increase the risk of venous thromboembolism and bleeding [35,36]. Venous thromboembolism in cancer patients can cause unnecessary hospitalisations, interruption or postponement of cancer treatment, and increased mortality, leading to decreased quality of life and increased costs. The model was designed based on the SELECT-D trial. Rivaroxaban was compared to LMWH (the current standard of care in patients with cancer experiencing VTE) over a time horizon of five years. The treatment duration was six months based on the SELECT-D trial design. Rivaroxaban appeared to be a cost-saving treatment option with a health benefit of 0.012 QALYs per patient over five years when compared to an LMWH. The cost-savings were mainly driven by the difference in drug costs, since LMWHs are more expensive than DOACs.

For all three subgroups (patients with atrial fibrillation undergoing electric cardioversion, patients requiring extended anticoagulation for the prevention of venous thromboembolism and cancer patients experiencing venous thromboembolism) we can conclude that the use of DOACs is cost-effective or cost-saving compared to the current standard of care. Ergo, cost-effectiveness for subgroups seems not to differ from that found in the main indicated groups. Cost-effectiveness analyses for the use of DOACs in specific subgroups that may have been excluded from the initial registration trials can be used in post-reimbursement decisions—such as clinical guideline updates—that may broaden the implementation of DOACs.

Was a conservative introduction of DOACs justified based on the argument of high costs?

The Health Council of the Netherlands opted for a gradual and conservative introduction of DOACs on the basis of their high budget impact and the lack of RWD. However, there are a number of other explanations for the wish to have a conservative introduction of the DOACs. Anticoagulation is known for its high risk of hospitalisation related to adverse

events (i.e., bleeding) or the recurrence of thromboembolic events in case of non-optimal effect. For VKAs, there is a lot of experience and clear corresponding guidelines on how to handle these events. Initially, the reversal of bleeding was more difficult with DOACs because of the lack of an antidote. In the meantime, antidotes have been developed and become available [37,38]. Moreover, the first clinical trials excluded old and fragile patients, and patients with a known high bleeding risk. Therefore, also because of that aspect, physicians may have been hesitant to prescribe DOACs.

The withdrawal of the first DOAC introduced to the European market may have influenced the introduction of DOACs in general. The application for market authorisation of ximelagatran (Exanta®) was withdrawn in 2006 because new patient safety data showed a potential risk of serious liver injury. As a result, the liver function in patients using dabigatran—introduced in 2008—had to be closely monitored. Later, it emerged that liver function monitoring is not necessary with the four DOACs currently on the European market. Another influencing factor may have been that the Netherlands—in contrast to other countries—has a specialised thrombosis service in place to monitor the INR in patients treated with VKAs. Therefore, there was not just the introduction of a new drug; it was also an adjustment of the healthcare system to incorporate the new drugs, which takes time.

Although there were explanations why the introduction of the DOACs should have been conservative, it can be questioned whether we have been maybe a bit too cautious: more and more RWD show that DOACs are at least as effective and safer compared to VKAs in patients with atrial fibrillation and venous thromboembolism, confirming initial findings from the trials. Moreover, the results of both the cost-effectiveness analyses presented in this thesis and the results from other cost-effectiveness studies show that DOACs are likely to be cost-effective or even cost saving in the Netherlands. However, and likely, the fear of a high budget impact has hampered immediate large-scale introduction.

In the meantime, the DOACs have become important drugs all over the world. In 2015, dabigatran was added (as, later, were the other three DOACs) to the list of essential medicines of the World Health Organisation [39]. In the Netherlands, prescriptions of DOACs have increased enormously over the last couple of years. For the first time, the number of patients treated with a DOAC is higher than the number of patients treated with a VKA [40]. In hindsight, on the basis of cost-effectiveness, there was no reason for a conservative introduction of DOACs. Obviously however, reasoning in hindsight is easier than predict with some level of certainty.

Conclusion

Based on the chapters and the other cost-effectiveness analyses conducted specifically for the Dutch situation, it can be concluded that the use of DOACs is cost-effective compared with VKAs for patients with atrial fibrillation. DOACs are likely to be cost-saving for patients experiencing venous thromboembolism who need temporary (3–24 months) anticoagulation. The main limitations of using RWD for the validation of trial-based cost-

effectiveness results are related to differences in study design and population between trial and real-world studies. This makes the comparability of the cost-effectiveness results challenging. In practice, there are some specific subgroups that may have been excluded in the initial registration trials. Nevertheless, the RWD-based cost-effectiveness studies in this thesis do confirm the trial-based cost-effectiveness results, implying that DOACs are cost-effective when used in a real-world situation. In patients with atrial fibrillation undergoing cardioversion, patients with very high VTE recurrence risk requiring continuous anticoagulation, and cancer patients experiencing VTE, DOACs also appeared to be cost-saving or cost-effective. In hindsight, on the basis of cost-effectiveness, there was no reason for a conservative introduction of DOACs. Nevertheless, the budget impact of DOACs remains high, but this is likely to reduce over time due to a reduction in costs of the thrombotic service and expiration of the patents. It is not possible to make any conclusions as to which DOAC is preferred for each indication or subgroup. Future research directly comparing the DOACs should provide more clarity on this matter and potentially enhance personalised DOAC use.

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